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09/281,717	03/30/1999	JOHN D. BAXTER	9811-008-999	7561

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EXAMINER
MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
1631	33

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/281,717	BAXTER ET AL.	
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE f this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002 and 07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 30-43* is/are pending in the application.

4a) Of the above claim(s) *34-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *18 November 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. All objections and rejections not repeated below are hereby withdrawn.

Election/Restrictions

The restriction requirement mailed 2/6/03 was made in error and is hereby withdrawn. The examiner apologizes for the error and any confusion resulting therefrom. Arguments made in the response of 4/7/03, as they apply to the restriction set forth below, are addressed below.

Newly submitted claims 34-43 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: original claims 1-16 recited a method of identifying a compound which binds to a coactivator binding site of a nuclear receptor, specifically a human thyroid receptor. A method using atomic coordinates and performing a binding assay with a receptor other than the human thyroid receptor necessarily requires different method steps (e.g. modeling compounds which fit into the binding site of a different receptor), use of different compounds (i.e. the different receptor), and would be expected to give different results than would a method using the human thyroid receptor, therefore claims 34-43 recite separate and distinct methods from those of claims 1-16 and 30-31. In addition, a search for a method using the human thyroid receptor is necessarily different from a search for a method using any other receptor. It is noted, as argued by applicant in the response filed 4/7/03, that original claim 9 limited a nuclear receptor to be one from the general classes of retinoids, peroxisomes, vitamin D, estrogens, and others. However, original claim 9 depends from any of claims 5-8, wherein claims 5-8 specifically recite coordinates identified by alignment with a human thyroid receptor. None of claims 1-16 or 30-31 (i.e. those originally presented) recited identifying coordinates by homology to any receptor other than the human thyroid receptor. None of the originally presented claims recited the specific receptors or SEQ

ID NO's recited in the newly presented claims. A search for a method wherein a model comprises coordinates identified by homology to a human thyroid receptor is necessarily a different search from a similar method wherein coordinates are identified by homology to a different receptor. In addition, a search for any sequence (structural product) is necessarily a different search from that for any other sequence. For these reasons, applicant's arguments are not persuasive and claims 1-16 and 30-31 are separate and distinct from each of the methods recited in claims 34-43. New claims 32-33 are directed to the same subject matter as that of original claims 1-16 and 30-31 and are therefore also considered to be elected.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34-43 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Drawings

The corrected or substitute drawings were received on 11/18/02. These drawings are acceptable to the examiner.

Specification

The amendment to the specification filed 11/19/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

(a) the amendment to page 41 recites that the structure in Appendix 2 consists of "a portion of human ERα chain A and chain B", "two molecules of DES", and "two molecules of

GRIP-1 NR-box 2 peptide...." The title of originally filed Appendix 2 states "Atomic Coordinates for ERα Complexed with DES, and a GRIP1 NR-box 2 Peptide." Unlike Appendix A, which identifies the chains therein in REMARKS, Appendix 2 does not provide any identification of the data other than that provided in the title. The originally filed specification, on page 41, disclosed that "Atomic coordinates of a DES-LBD-peptide complex are attached as Appendix 2" but does not otherwise describe the data in Appendix 2. It is noted that residues labeled "A" in Appendix 2 include those designated "DES" and "CL" while residues labeled "B" include those designated "DES" and "CBM". It is further noted that all residues labeled "DES" are numbered "600." As one skilled in the art would not be able to deduce, merely by looking at Table 2, what proteins, peptides, or portions thereof, are represented by residues labeled A, B, C, and D, nor that the residues represent TWO molecules of DES and TWO molecules GRIP1 NR-box 2 peptide, the added description of Appendix 2 on page 41 contains new matter;

(b) the amendment to the sequence listing, filed 11/19/02, contains SEQ ID NO: 52 and SEQ ID NO: 53, which are 251 and 250 residues in length, respectively. According to the amendment on page 36, SEQ ID NO: 52 corresponds to chain A and SEQ ID NO: 52 corresponds to chain B of Appendix A. Each of Chain A and Chain B of Appendix A consists of atoms numbered 211-461; i.e. 251 residues. As chain B and SEQ ID NO: 53 are not the same in length, newly filed SEQ ID NO: 53 is not supported by the original disclosure of Appendix A, and is therefore new matter;

(c) the amendment to the sequence listing also contains SEQ ID NO: 59, which is 246 residues long, and SEQ ID NO: 60, which is 11 residues long. The amended specification discloses, on page 41, that SEQ ID NO: 59 corresponds to chain D of Appendix 2. Chain D of Appendix 2 consists of 11 amino acids and therefore does not appear to correspond to SEQ ID NO: 59. The amended specification also discloses, on page 43 that Appendix C contains

coordinates for ERα corresponding to SEQ ID NO: 60. The part of Appendix 3 which appears to represent atomic coordinates for ERα is numbered 306-55; i.e. 246 residues. Upon cursory review, SEQ ID NO: 60 appears to find support in the disclosure of chain D of originally filed Appendix 2, and is not new matter. However, it is not clear if SEQ ID NO: 59 is supported by the originally filed specification (including appendices) or claims, therefore SEQ ID NO: 59 is new matter. It is possible that a typographical error in assigning SEQ ID NO's was made, but until the error is corrected and specific support for the amended matter is supplied by applicant, SEQ ID NO: 59 is considered new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

The disclosure is objected to because of the following informalities: on page 41, chain D is represented by SEQ ID NO: 60, not, as incorrectly set forth in the instant specification, by SEQ ID NO: 59. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 2-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2-8, the use of parentheses renders the claim indefinite because it is unclear whether the limitations within the parentheses are part of the claimed invention. See MPEP § 2173.05.

Each of claims 2-8 recites "a portion of human thyroid beta receptor (SEQ ID NO: 52 or SEQ ID NO: 53)". It is unclear if applicant intends the human thyroid beta receptor to correspond to both of the recited SEQ ID NO's, only one SEQ ID NO, or intends that "a portion"

of the receptor correspond to one or both of SEQ ID NO's 52 and 53. As it is unclear whether the entirety or merely a portion of the human thyroid beta receptor is intended to correspond to the recited SEQ ID NO's, the claims are indefinite.

Each of claims 2-8 recites alignment with residues of a human thyroid beta receptor, wherein the residues are limited to be selected from a recited group, and also recites specific SEQ ID NO's, which presumably correspond to either a portion or the entirety of the receptor (see above). If the SEQ ID NO's are intended to represent a portion of the receptor, then it is further unclear if the groups of residues recited in each claim are limited to be those found on the portion corresponding to the SEQ ID NO: I.e. it is unclear whether one or both of the SEQ ID NO: must comprise the recited residues). For this reason, the claims are further indefinite.

It is unclear what limitation(s) is/are intended, if any, by the newly recited SEQ ID NO's in claims 2-8, but it is clear that the receptor is intended to be limited to one comprising at least one of a group of amino acids specifically recited in each claim. Therefore, for purposes of applying the prior art, the claims will be interpreted as if they recited residues of any portion of a human thyroid beta receptor wherein a residue is selected from the group recited in each pending claim.

Claim Rejections - 35 USC § 102

Claims 1-10, 12-15, and 30-33 are rejected under 35 U.S.C. 102(e) as being anticipated by SCANLAN et al. (US 6,26,622, filed Dec. 13, 1996).

SCANLAN teaches a method of identifying a compound which selectively modifies the activity of a nuclear receptor (i.e. a coactivator), specifically a thyroid receptor, or of identifying an agonist or antagonist, by using the atomic coordinates of the receptor, specifically its ligand binding domain (LBD) to model compounds which fit spatially into the LBD using a computer,

screening the test compounds in an in vivo or in vitro assay, then identifying the test compound which selectively modifies activity of the receptor or is an agonist or antagonist (col. 9, line 59-col. 10, line 36), thereby anticipating claims 1, 9-10, 12, and 30-31. SCANLON specifically teaches that his antagonists or agonists can block or promote binding of a coactivator (col. 24, lines 45-65), and teaches that chemical moieties (on ligands) may be modeled/designed such that interactions of a second chemical on the natural hormone (i.e. hormone dependant binding) may be decreased or increased (col. 2, lines 23-34), thereby anticipating claims 14 and 32-33. SCANLON teaches that his compounds may be peptides, peptidomimetics, or synthetic compounds (col. 3, lines 63-65), or may be from a collection of compounds designed around a scaffold (i.e. a library; col. 32, lines 39-48), thereby anticipating claims 14-15. SCANLON specifically teaches fitting of compounds to TR-beta wherein the atomic structural model of TR-beta comprises coordinates for amino acids Ile280, Thr281, Val283, Val284, Ala287, Lys288, Phe293, Gln301, Ile302, Leu305, Lys306, Cys309, Pro453, Glu457, Val458, Phe459 (Appendices 7 and 8), thereby anticipating claims 2-8.

Applicant's arguments filed 11/18/02 have been fully considered but they are not persuasive. In response to the argument that SCANLAN does not specifically teach the structure of a coactivator binding site, it is noted that applicants admit on page 16 of the response that a coactivator binding site is "a specific part of the LBD"; i.e. that the ligand binding domain (LBD) inherently comprises a coactivator binding site. Applicants also admit on pages 16-18 of the response that SCANLAN does teach identification of compounds which bind in the LBD by atomic structural modeling. SCANLAN teaches that the compounds identified in his method are those which "selectively modify" the activity of a thyroid receptor. As the LBD inherently comprises a coactivator binding site, as admitted by applicants, and as compounds which result in an increase in activity may be considered coactivators, the examiner maintains

that SCANLAN inherently teaches a method of identifying compounds which bind to a coactivator binding site of a nuclear receptor.

Claim Rejections - 35 USC § 103

Claims 1-15 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over SCANLAN *et al.* (US 6,266,622) in view of KUNTZ *et al.* (IDS document: Science 257, pp. 1078-1082. (1992)).

Applicant's arguments filed 11/18/02 have been fully considered but they are not persuasive. Applicant argues that SCANLAN does not teach the structure of a coactivator binding site, nor the constituent amino acids therein, and that KUNTZ does not supply this lack. In response, the examiner maintains that SCANLAN's teaching for the atomic structure and modeling thereof, of the LBD of a thyroid receptor, necessarily includes modeling of the atomic structure of a coactivator binding site, as set forth above. As KUNTZ is relied upon for a teaching of high throughput screening, not for atomic coordinates, the fact that KUNTZ does not supply atomic coordinates is moot.

Claim 1 recites a method of identifying a compound which binds to a coactivator binding site of a nuclear receptor wherein test compounds are fit into the binding site using an atomic structural model of the receptor's coactivator binding site or portion thereof, screening the test compounds in a binding assay and identifying compounds that bind to the coactivator binding site. Claims 2-8 limit the atomic structural coordinates. Claim 9 limits the receptor. Claims 10 and 12 limit the binding assay to an in vitro or in vivo assay. Claim 11 limits the screening to high throughput screening. Claims13-15 limit the test compound. Claims 32-33 further limit the test compound of claim 14 to be one which promotes or inhibits hormone-dependant coactivator binding to the receptor. Claim 31 limits the method to one wherein the atomic

coordinates are provided to a computerized modeling system. Claim 30 recites a compound identified by the method.

SCANLAN teaches a method of identifying compounds which bind to a ligand binding site on a thyroid receptor and alter the activity of the receptor (e.g. a coactivator), as set forth above. SCANLAN does not teach high throughput screening.

KUNTZ teaches use of high throughput screening in combination with computer screening/modeling to identify ligands for various proteins (pp. 1080-1081). KUNTZ specifically teaches that robotic systems make it feasible to scan entire databases of compounds (p. 1078).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used the high throughput, robotic screening of KUNTZ in the method of SCANLAN where the motivation would have been to screen large numbers of compounds in a method to identify coactivators, as suggested by KUNTZ' teaching that lead discovery (e.g. of drug candidates) will proceed more rapidly by combining computer screening and high volume (throughput) assays (p. 1081). One skilled in the art would reasonably have expected success in combining the high throughput assays of KUNTZ with the method of SCANLAN because both teach combining test assays with computer modeling/screening steps, and both teach that such assays can be used to identify compounds which bind to receptors.

Claims 1-10, 12-16, and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over SCANLAN *et al.* (US 6,266,622) in view of HEERY *et al.* (IDS document: Nature (1992), vol. 387, pp. 733-736).

Applicant's arguments filed 11/18/02 have been fully considered but they are not persuasive. Applicant argues that SCANLAN does not teach the structure of a coactivator binding site, nor the constituent amino acids therein, and that HEERY does not supply this lack.

In response, the examiner maintains that SCANLAN's teaching for the atomic structure and modeling thereof, of the LBD of a thyroid receptor, necessarily includes modeling of the atomic structure of a coactivator binding site, as set forth above. As HEERY teaches specific sequences/structures on coactivators which are necessary for binding to LBD's on receptors, and applicants admit that an LBD, such as that taught by SCANLAN, necessarily comprises a coactivator binding site, the examiner maintains that it would have been obvious to have used peptides comprising the LxxLL motif taught by HEERY in the method of SCANLAN for the reasons and motivations set forth below.

The claims recite a method of identifying a compound which binds to a coactivator binding site of a nuclear receptor, as set forth above. Claim 16 limits the test compound to be a peptide comprising a nuclear receptor box.

SCANLAN teaches a method of identifying compounds which bind to a ligand binding site on a thyroid receptor and alter the activity of the receptor (e.g. a coactivator), as set forth above. SCANLON does not specifically teach peptides comprising nuclear receptor boxes.

HEERY teaches motifs comprising an LxxLL sequence which are necessary and sufficient for binding of coactivators to ligand binding domains of nuclear receptors (p. 733, abstract). As HEERY teaches motif sequences which are identical to those exemplified by applicant as being "nuclear receptor boxes" (See instant Figure 7 and the TIF2 sequences taught by HEERY on p. 735, Figure 2a), the motifs taught by HEERY are interpreted to be "nuclear receptor boxes".

It would have been obvious to one of ordinary skill in the art at the time of invention to have used peptides comprising the LxxLL motif taught by HEERY as the test compounds in the method of SCANLAN where the motivation would have been to enhance success in identifying coactivators by screening peptides comprising a sequence/motif already known to be present in

known coactivators of nuclear receptors, as suggested by the teaching of HEERY that an LxxLL motif is both necessary and sufficient for binding of coactivators to nuclear receptors (p. 734). One skilled in the art would reasonably have expected success in screening peptides comprising the LxxLL motif of HEERY in the method of SCANLAN because SCANLAN teaches that peptides may be screened in his method and HEERY teaches that peptides comprising his motif can be screened for binding/coactivator activity (p. 735, Figure 3).

Conclusion

Claims 1-16 and 30-33 are rejected; claims 34-43 are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3524.

MARJORIE MORAN
PATENT EXAMINER

mam
July 14, 2003